UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**Note to Reader**
**January 15, 1998**

**Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.**

**The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.**

**There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.**

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

**Note:** This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket ( RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **Phosmet [(mercaptomethyl) phthalimide S-(O,O-dimethylphosphorodithioate]:** Hazard Identification Committee Report.

CASRN: 732-11-6
PC Code: 059201
Caswell: 543

FROM: George Z. Ghali, PhD.
Executive Secretary, Hazard Identification Committee.
Health Effects Division (7509C)

Thru: Clark Swentzel
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

To: Susan Lewis, Chief PM 03
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on September 04, 1997 to evaluate the existing and/or recently submitted toxicology data in support of phosmet re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose (RfD) for this chemical.

Phosmet had already been evaluated by the HED-RfD Committee on March 3, 1994 (report dated May 11, 1994). Therefore, this Hazard Identification Committee report should be considered in conjunction with the RfD-Committee report of May 11, 1994.

Material available for review consisted of data evaluation records (DERs) for combined chronic toxicity-carcinogenicity studies in rats **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a subchronic study in rats **(82-1a)**, and a battery of mutagenicity studies **(84-2)**.

INDIVIDUALS IN ATTENDANCE

Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, Melba Morrow, Kathleen Raffaele, John Redden, and Clark Swentzel (Chairman, Hazard Identification Committee, HED).

In attendance also were Stephen Dapson and Christina Swartz, HED, as observers.

Hazard Identification Committee member(s) in absentia: Jess Rowland.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

William Greear William Greear

# HAZARD IDENTIFICATION

Based on comprehensive evaluation of the toxicology data available on phosmet, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the hazard categories indicated below:

I) Dietary Hazard resulting from ingestion of residues of this particular pesticide when used on agricultural food commodities for pest control purposes or as a food additive and may include **acute and/or chronic exposure**,

II) Occupational/Residential Hazard resulting from **dermal and/or inhalation** exposure to the chemical and may include short-, intermediate- and/or long-term exposure.

Issues related to the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) are also addressed.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable duration extrapolation are also addressed.

Based on the use pattern/exposure profile, the Committee determined that the risk assessments indicated below are required for phosmet.or as otherwise stated.

## I. Dietary Exposure

### A. Acute Dietary Exposure:

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No: 41916401.

In a [redacted]ar chronic toxicity/carcinogenicity study (MRID 41916401) [redacted]met was administered to Sprague-Dawley Crl:CD(R) SD BR rats in the diet at 20, 40, 200 or 400 ppm (equivalent to 1.1, 1.8, 9.4 and 23 mg/kg/day in males and 1.1, 2.1, 10.9 and 27 mg/kg/day in females) for 2 years. The 400 ppm group was terminated at 12 months.

At 20 ppm there was marginal RBC cholinesterase (ChE) inhibition (16%) noted at 6 months in males only. At 40 ppm RBC

(about 15-20%) and serum ChE (5-36%- M; 15-25%- F) was inhibited in both males and females. Brain cholinesterase was inhibited (>34%) in males and females at 200 ppm. The **NOEL** for cholinesterase inhibition was < 20 ppm and the **LOEL** was ≤ 20 ppm based on RBC ChE in males (marginal - only at 6 months).

Systemic toxicity was limited to increased incidence of fatty change in the liver of males at all doses. In addition, at 200 ppm and above (males) there were increases in the incidences of depressed hepatic foci, hyperkeratosis of the stomach; (females) fatty change in the liver, mineralization of the thyroid. At 400 ppm (males and females) body weight and body weight gain were decreased; (females) decreased kidney weight and increased BUN. The systemic toxicity **NOEL** is < 20 ppm and the **LOEL** is ≤ 20 ppm based on an increased incidence of fatty change in the liver of males.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF):** An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. An additional UF of 3 was recommended for FQPA considerations for the lack of acute and subchronic neurotoxicity studies in rats.

A full characterization of the neuropathological potential for phosmet is not available. Positive results from these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. These studies are considered a data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

**Comments and Rationale:** Although the chronic toxicity study in rats is a long-term study, it was considered appropriate for risk assessment for acute exposure since the endpoint selected (cholinesterase inhibition) occurs in the study as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies.

**Supportive Data:** The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study. In this two-generation reproductive toxicity study conducted in Sprague-Dawley (Crl:CD SD BR) rats, parental toxicity consisted of RBC cholinesterase inhibition at 20 ppm (6-16%), 80 ppm (>37%), and 300 ppm (>74%). Serum cholinesterase was inhibited at 80 ppm (34%) and 300 ppm (65%). There were clinical signs (tremors) noted at 300 ppm). The parental **LOEL** is equal to or less than 20 ppm. The parental **NOEL** is equal to 20 ppm. Reproductive toxicity consisted of decreased fertility, number of live pups/litter, pup weights, lactation index and



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fertility index (e.g., 88% versus 48%, control and high dose). The reproductive **NOEL** is 20 ppm, and the reproductive **LOEL** is 80 ppm based on decreased fertility.

**B. Chronic Dietary Exposure-Reference Dose (RfD):**

**Reference Dose ($R_fD$):** 0.003 mg/kg/day.

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No: 41916401.

**Endpoint and Dose Level Selected for use in risk assessment:** NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF):** An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The use of a UF of 100 was justified based on the availability of a chronic toxicity study in a second species (MRID No. 00062651, 00075419, 00076436, 00080431, 00080556) and a reproductive toxicity study in rats (MRID No. 41520001) in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group. Pursuant to the FQPA, an additional UF of 3 was recommended to account for the lack of acute and subchronic neurotoxicity studies in rats (see Section I-A, above).

**Comments and Rationale:** This is a chronic feeding study and is considered, by definition, to be most appropriate for establishing the RfD for this chemical.

## II. Occupational/Residential Exposure

**A. Dermal Exposure:**

The Committee estimated that the dermal absorption rate is about or no greater than 10%. This conclusion was based on the findings of a dermal absorption study in rats (MRID 40122201).

In this dermal absorption study , phosmet (Imidan 50-WP, 50% a.i., Lot [redacted] RSEE 300 10) was applied to the shaved skin on the back of 4[redacted] Sprague-Dawley (CD) rats/group. Dilutions used were 1:2[redacted] and 1:100 applied at a rate of 300 $\mu$l rat. Administe[redacted]oses were 2.67, 0.52 and 0.058 mg/cm$^2$ skin. The dosing solutions contained 20-50 uCi of labeled compound. The radioactive test material had a specific activity of 26.6 mCi/mmol and was 97% pure. Phosmet was poorly absorbed when applied to the shaved skin of rats. The percent of radioactive dose found in the carcass, skin, urine, feces, and blood (combined) after 24 hours was 0.9, 3.8, and 11.8% of administered doses of 0.67, 0.5% and 0.058 mg/Cm skin, respectively. The skin

at the dosing site contained much of the radioactivity. The amount in the carcass and excreta reached a maximum at 24 hours and accounted for 7.9, 1.7 and 0.3% of the administered radioactivity at the low-, mid- and high-doses, respectively. Excretion of the absorbed radioactivity was primarily urinary; 0.1% of the high-dose (1:2 dilution), 1.1% of the mid-dose (1:10 dilution), and 5.4% of the low dose (1:100 dilution) radiolabel was found in the urine between 10 and 24 hours. Much lesser amounts were found in the feces.

1. Short Term Dermal Exposure (1-7 days):

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No.: 41916401.

For more information and/or the executive summary of the study selected for this risk assessment, See Section I-A, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** NOEL = 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF):** Same as Section I-A, above.

**Comments and Rationale:** Although this study is an oral long-term study, it was considered appropriate to use for the dermal risk assessment for short-term exposure since the endpoint selected (cholinesterase inhibition) occurs as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies. Furthermore, the acute dermal toxicity studies available on this chemical do not cover the duration of 1-7 days and were conducted on rabbits. The rabbit is considered inappropriate for dermal testing of thiophosphate, phosphorothioate and phosphorodithioate compounds which require metabolic activation to the corresponding phosphates by microsomal enzymes. Since an oral toxicity study is used in this risk assessment, a dermal absorption rate of 10% should be considered in the calculation of the dermal equivalent dose.

**Supportive Data:** The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section I-A, above).

2. Intermediate-Term Dermal Exposure:

**Critical Study:** Chronic toxicity study in rats (83-1a), MRID No(s): 41916401.

**Executive Summary:** See Section I-A, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** NOEL



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= 1.1 mg/kg/day, based on RBC and serum cholinesterase inhibition observed at the next higher dose level of 1.8 mg/kg/day.

**Uncertainty Factor (UF)**: Same as Section I-A, above.

**Comments and Rationale**: Although the chronic toxicity study in rats is a long-term study, it was considered appropriate for use in risk assessment for the shorter duration exposure since the endpoint selected (cholinesterase inhibition) occurs in the study as early as 2-4 weeks and because the NOEL/LOELs are lower than those in the rat subchronic studies. The 21-day dermal toxicity study available on this chemical was conducted in rabbits. The rabbit is considered inappropriate for dermal testing of thiophosphate, phosphorothioate and phosphorodithioate compounds which require metabolic activation to the corresponding phosphates by microsomal enzymes.
**Supportive Data**: The Committee recommended the use of the reproductive toxicity study in rats (MRID No. 41520001) as a supportive study (see executive summary under Section II-B, above).

3. Long-Term Dermal Exposure:

Based on the use pattern and exposure profile, the Committee determined that this type of risk assessment may not be required.

**B. Inhalation Exposure:**

Since there are no inhalation studies available for use in inhalation risk assessment, the Committee recommended the use of an absorption rate of 100% of the inhalation exposure estimates for each exposure duration.

**C. Aggregate Risk:**

Because of common endpoints for different routes of exposure, the non-cancer aggregate risk for phosmet can be expressed based on the following equation:

Aggregate Risk = the inverse of $1/MOE_{(dietary)} + 1/MOE_{(inhalation)} + 1/MOE_{(dermal)}$

**III. FQPA Considerations:**

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to ... "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate

exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for phosmet was evaluated by the Hazard Identification Committee. The Committee concluded the following:

**Adequacy of data:** The reproductive and developmental toxicity issues had been recently addressed by the HED-RfD Committee (report dated May 11, 1994). The data base for phosmet included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. However, because of the lack of the necessary information, required to assess the need for a developmental neurotoxicity study in rats, it was determined that a data gap exists for the assessment of hazard to infants and children.

**In an attempt to develop a weight-of-evidence recommendation on the need for developmental neurotoxicity testing with phosmet, the following information were considered:**

Phosmet is a neurotoxic organophosphate associated with plasma, RBC and brain cholinesterase inhibition in various species. According to the Health Effects Division record (toxicology one-liner), phosmet was associated with acute delayed neurotoxicity in hens, and a positive effect on neurotoxic esterase. The delayed neurotoxic response was not, however, repeated in subsequent studies.

No a[redacted]te comparative characterization of the cholinest[redacted] inhibition has been conducted in pregnant females or their offspring or in adult and neonatal animals.

Phosmet may cause, also, disruption of neuroendocrine functions, as evidenced by some reductions in fertility, mating performance in the two-generation reproduction study in rats, reduced testes and ovary weights, and histopathological evidence of moderately decreased spermatogenesis. Reproductive function was impaired more severely in the second generation than the

first. Furthermore, acute and subchronic neurotoxicity studies in rats have not yet been submitted.

On the other hand, there were no evidence of developmental anomalies or abnormalities in the development of the fetal nervous system observed in the prenatal developmental toxicity studies in either Wistar rats or New Zealand white rabbits, at maternally toxic doses. and no evidence of alterations to brain weight or histopathology was observed in the chronic toxicity studies in rats, mice, and dogs.

Based on the above, the Committee agreed that there was insufficient data to determine the need for a developmental neurotoxicity in rats. Such a determination would depend on the results of an acute and/or subchronic neurotoxicity study in rats, in particular, upon the neuropathology data, which are more sensitive in detecting treatment-related effects than the data from a standard subchronic or chronic study. Neither of these two neurotoxicity studies has been submitted to the Agency yet.

The inability to assess the need for a developmental neurotoxicity study is considered a potential data gap for the assessment of hazard to infants.

**Susceptibility:** The available data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to phosmet.

**Uncertainty factor:** The inability to assess the need for a developmental neurotoxicity study is considered a potential data gap for the assessment of hazard to infants and children.

The Committee evaluated the data as described and concluded that the 10-fold uncertainty factor for the protection of infants and children can be reduced to 3-fold. This decision to reduce the 10-fold uncertainty factor to 3-fold was based on the following:

On one hand, the data base, which includes acceptable developmental toxicity studies in two species and a two-generation reproduction study in rats, demonstrate no evidence of increased sensitivity to young animals following pre- and/or post-natal exposure to phosmet. Furthermore, results from studies conducted to evaluate the potential for delayed neurotoxicity and neurotoxic esterase assays did not support classification of phosmet as a delayed neurotoxicant.

On the other hand, since acute and subchronic neurotoxicity studies in rats have not been submitted to the Agency at the time of this review, a full characterization of the neuropathological potential for phosmet is not available. Positive results from



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these studies could potentially lead to a data requirement for a developmental neurotoxicity study in rats. These studies, i.e. the acute and subchronic neurotoxicity studies in rats, are considered a data gap for the assessment of hazard to infants and children, for which a 3-fold uncertainty factor was recommended.

IV. Carcinogenicity:

The carcinogenicity issue has been discussed by the Health Effects Division-Cancer Peer Review Committee. The Committee agreed that "phosmet should be classified as a "Group C", possible human carcinogen, and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk".

"This decision was based on an increased incidence of liver tumors in male B6C3F1 mice at the high dose, that was statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset. Female mice had a significant dose-related trend for liver tumors, and for mammary gland adenocarcinomas, as well. There was no evidence for carcinogenicity in an acceptable study in rats"

The mutagenicity issue has been addressed as part of the weight of the evidence evaluation of the carcinogenic potential of this chemical. Phosmet was determined to be a potent, direct-acting mutagen (report dated May 25, 1994).

cc: Stephanie Irene
Clark Swentzel
William Burnam
William Greear
Christina Swartz
Michael Metzger
Karen Whitby
Jess Rowland
Amal Mahfouz (OW)
Hazard ID file
Caswell File



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